Online supplement

Long term mortality and hospital resource use in ICU patients with alcohol-related liver disease

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Supplementary methods

Definition of comorbidities in severe comorbid comparator cohort

The comparator cohort with other severe comorbidities comprised patients with severe cardiovascular, respiratory or renal disease. Patients with alcohol-related liver disease, but not other types of liver disease, were excluded from the control cohort. These are defined by SICSAG based on the APACHE system as follows:(1)

Severe cardiovascular disease: specifies whether the patient has fatigue, claudication, dyspnoea or angina at REST. Where any activity increases symptoms, symptoms must be due to myocardial or peripheral vascular disease. Functionally, this patient cannot stand alone, walk slowly or dress without symptoms. Definition equals the New York Heart Association, Class IV.

Severe respiratory disease: specifies whether the patient has permanent shortness of breath with light activity, due to pulmonary disease. Functionally, this patient is unable to work and has shortness of breath performing most normal activities of daily living (e.g. walking 20 metres on level ground, walking slowly in the house, climbing one flight of stairs; or dressing or standing).

Severe renal disease: the patient currently requires chronic renal replacement therapy (chronic haemodialysis, haemofiltration or peritoneal dialysis) for irreversible renal disease.

Derivation of matched cohort of general ICU patients

The ALD cohort was matched to a cohort of general ICU patients using coarsened exact matching (CEM) method.(2) This method aims to reduce imbalance between two cohorts whilst maximising the number of matched observations. Instead of traditional 1-to-1 matching, CEM employs an algorithm to match within strata of user-determined ranges of values for each variable, the boundaries of which are 'coarsened' to maximise matching. CEM matches observations that are within the same strata for every variable that is included in the match. Therefore, CEM ensures that matched patients have values within a similar range for each variable of interest, though this does not need to be exact. Categories were increasingly widened on iterations of the matching algorithm to maximise matches. The cohorts were matched without replacement on the following variables on the first iteration: age (quartiles), sex, Acute Physiology Score (quartiles with missing category), admission source (theatre vs other), socioeconomic status (quintiles) and comorbidity count (0 vs 1 or more).

Databases

The databases used in the study (Scottish Intensive Care Society Audit Group (SICSAG), Scottish Morbidity Record of acute hospital admissions (SMR01) and Scottish death records) are subject to

regular quality assessment procedures. The most recent report published by the NHS in Scotland showed that diagnostic coding in the SMR01 (hospital dataset) has a 88.3% accuracy compared with case-note review for the main diagnosis field, and 82.1% accuracy for additional diagnoses (see reference 16 in Main Manuscript). Similarly, the SICSAG dataset is subject to validation by point of data entry, case-note validation and central validation. Both diagnosis and Chronic Health Evaluation fields are subject to case-note validation (see reference 17 in Main Manuscript).

Variables

Variables available in the two datasets included demographics/pre-admission factors (age, sex, socioeconomic status, number of hospital admissions in the year before index admission, Charlson/SICSAG defined comorbidities (see reference (3) for details of derivation) and factors relating to the ICU and hospital stay (admission source, admission diagnosis, APACHE II score, Acute Physiology Score (APS), organ support during first 24 hours, highest bilirubin in the first 24 hours, ICU length of stay, hospital length of stay). For comparisons between ALD and comorbid comparator cohort, a count of comorbidities excluded the index comorbidity (e.g. ALD cohort members could not have 'liver disease' as a comorbidity). For comparisons between ALD and matched general ICU cohorts, all ALD cohort members were defined as having at least one comorbidity due to liver disease. ICU admission diagnosis was grouped by organ system for ALD vs comorbid comparator cohort comparisons. In models identifying independent predictors of outcomes for the ALD cohort, the six most common APACHE admission diagnoses in the ALD cohort were grouped with a seventh 'other' category containing remaining diagnoses. Continuous variables were categorised if linearity assumptions were not valid. Cirrhosis was defined in the ALD cohort by the presence of diagnosis codes in any of the following fields: relevant ICD-10 codes in diagnosis fields in the SMR01 hospital database (cirrhosis: K703 K740 K741 K742 K746; diagnoses likely to indicate underlying cirrhosis: ascites (R18), varices (I85 I864), portal hypertension (K766), hepatorenal syndrome (K767) and encephalopathy (G934); relevant codes in the SICSAG database (cirrhosis defined in APACHE chronic health evaluation comorbidities, variceal haemorrhage, hepatorenal syndrome, portosystemic shunt). For the subgroup analyses by ICU admission diagnosis, the four commonest admission diagnoses in the ALD and comparator cohorts were used (n(%) for each diagnosis for ALD, severe comorbid, matched general ICU cohorts): pneumonia (418 (17.0%), 622 (17.3%), 444 (18.6%)), septic shock (287 (11.7%), 329 (9.2%), 296 (12.4%)), post-cardiac arrest (108 (4.4%), 301 (8.4%), 178 (7.4%)), and acute abdominal pathology ((121 (4.9%), 471 (13.1%), 186 (7.8%)). Acute abdominal pathology comprised patients admitted with perforated viscus, bowel ischaemia, bowel obstruction or peritonitis.

Confounders

The following confounders were used to adjust multivariable models for comparisons between the ALD cohort and comparator cohort with other severe comorbidities:

> Age (linear), sex, SIMD quintile, number of inpatient admissions in year before index admission, ICU admission source, ICU admission diagnosis (organ system categories), Acute Physiology Score (linear), maximum number of organs supported (on first day of ICU admission for mortality outcome; on any day of ICU admission for readmission risk and resource use outcomes), count of comorbidities (see above).

Outcomes

The primary outcomes were 5-year mortality, emergency hospital resource use and cumulative risk of first hospital readmission obtained from linkage to Scottish death records and SMR01 registries. Emergency hospital resource was quantified as total number of emergency hospital admissions, total number of days spent in hospital, and total costs. Resource outcomes were reported per person-year alive and under follow-up. Per diem costs for hospital care were derived from the NHS Scottish Costs Book 2016/7.(4) Costs were converted from GB£ to US$ using Purchasing Power Parity 2017 rate (USD $1= GBP £0.703). Follow-up was censored on 01 January 2011 or after 5-year follow-up and commenced on ICU admission for mortality analyses and index hospital discharge for readmission/resource use analyses.

Cause specific readmission codes

ICD-10 codes for categories of causes of emergency readmission were as follows:

Liver disease	G934 I85 I864 R18 K70 K720 K721 K729 K740 K741 K742 K746 K766 K767 K769
Alcohol-related (non-liver)	E244 E512 F10 G312 G621 G721 I426 K292 K860 O354 P043 Q860 R780 T510 T511 T519 X45 X65 Y15 Y573 Y90 Y91 Z502 Z714 Z721
Other	All other ICD-10 codes

Statistical analysis

We used a significance level of 5% and 95% confidence intervals (CI). Confidence intervals for admission rates were derived assuming a Poisson distribution. Confidence intervals for days in hosptial and costs were derived using bootstrap methods (100 replications). All p values were two-sided. Appropriate measures of central tendency and dispersion were presented for continuous variables. A complete case analysis was undertaken. Missing liver SOFA score was included as an independent category. Comparisons between ALD and comparator cohorts were undertaken with

adjustment for confounders using the multivariable regression models: Cox regression (mortality); Fine and Gray regression (cumulative incidence of first emergency readmission); negative binomial regression (emergency admission rates). Clustering by health board of residence was accommodated by using robust cluster variance estimators for standard errors for regression coefficients and modelling health board by stratification (Cox) or as a fixed effect (Fine and Gray; negative binomial).

Supplementary references

1. SICSAG. Scottish Intensive Care Society Audit Group: WardWatcher (2014 version). Help pages: Definitions for all mandatory pages/fields. 2014 [cited 08/08/2017]Available from: http://www.sicsag.scot.nhs.uk/data/Help_042014.pdf
2. Blackwell M, Iacus S, King G, et al. CEM: Coarsened exact matching in Stata. Stata J 2009;9(4):524-546.
3. Lone NI, Gillies MA, Haddow C, et al. Five-Year Mortality and Hospital Costs Associated with Surviving Intensive Care. Am J Respir Crit Care Med 2016;194(2):198-208.
4. ISD. Scottish health services costs. 2017 [cited 08/08/2017]Available from: http://www.isdscotland.org/Health-Topics/Finance/Costs/

eTable 1. Baseline characteristics of ALD cohort and comparator matched general ICU cohort.
Cohort matched on age, sex, socioeconomic status, comorbidity count, and admission source.

		General ICU cohort	ALD cohort	p-value
n		2391	2391	
Age (years)	Median (IQR)	54 (45, 62)	53 (45, 61)	0.012
Sex	Male	1528 (63.9%)	1528 (63.9%)	1.0
	Female	863 (36.1%)	863 (36.1%)	
Socioeconomic status quintile	1 Least deprived	221 (9.2%)	224 (9.4%)	1.0
	2	277 (11.6%)	278 (11.6%)	
	3	392 (16.4%)	388 (16.2%)	
	4	523 (21.9%)	523 (21.9%)	
	5 Most deprived	978 (40.9%)	978 (40.9%)	
Comorbidity count	1	1889 (79.0%)	1889 (79.0%)	0.088
	2	351 (14.7%)	382 (16.0%)	
	3+	151 (6.3%)	120 (5.0%)	
Previous year inpatient hospital admissions	Median (IQR)	1.0 (0.0, 3.0)	1.0 (0.0, 2.0)	<0.001
	Mean (SD)	2.0 (2.5)	1.6 (2.5)	<0.001
Previous year inpatient days in hospital	Median (IQR)	5.0 (0.0, 15.0)	1.0 (0.0, 13.0)	<0.001
	Mean (SD)	14.0 (26.5)	11.1 (22.0)	<0.001
Admission source	Theatre after emergency surgery	379 (15.9%)	379 (15.9%)	<0.001
	Emergency department	648 (27.1%)	505 (21.1%)	
	Hospital ward	732 (30.6%)	746 (31.2%)	
	Other	632 (26.4%)	758 (31.7%)	
ICU admission diagnosis	Cardiovascular	651 (27.2%)	430 (18.0%)	<0.001
	Respiratory	824 (34.5%)	536 (22.4%)	
	Gastrointestinal/liver	322 (13.5%)	994 (41.6%)	
	Renal	93 (3.9%)	30 (1.3%)	
	Neurological	255 (10.7%)	275 (11.5%)	
	Trauma	39 (1.6%)	55 (2.3%)	
	Other	207 (8.7%)	71 (3.0%)	
Acute Physiology Score	Median (IQR)	17 (13, 22)	17 (12, 23)	0.21
APACHE II score	Median (IQR)	23 (17, 29)	22 (17, 28)	0.68
Number of organ systems supported on ICU admission	0	586 (24.5%)	370 (15.5%)	<0.001
	1	890 (37.2%)	1031 (43.1%)	
	2	765 (32.0%)	825 (34.5%)	
	3	150 (6.3%)	165 (6.9%)	
Mechanical ventilation	n (%)	1580 (66.4%)	1847 (77.3%)	<0.001
Circulatory support	n (%)	1030 (43.3%)	1098 (46.0%)	0.061
Renal replacement therapy	n (%)	260 (10.9%)	231 (9.7%)	0.155
Liver SOFA score	0	1478 (61.8%)	437 (18.3%)	<0.001
	1	246 (10.3%)	289 (12.1%)	
	2	174 (7.3%)	774 (32.4%)	
	3	33 (1.4%)	334 (14.0%)	
	4	10 (0.4%)	222 (9.3%)	
	Missing	450 (18.8%)	335 (14.0%)	
ICU length of stay (days)	Median (IQR)	2.5 (1.0, 6.6)	2.7 (1.0, 7.3)	0.18
Index hospital length of stay (days)	Median (IQR)	15.0 (6.0, 32.0)	12.0 (5.0, 29.0)	0.003
ICU mortality	n (%)	717 (30.0%)	1044 (43.7%)	<0.001
Hospital mortality	n (%)	936 (39.1%)	1398 (58.5%)	<0.001

Missing data Total (general ICU/ALD): admission source n=3 (0/3), organ support variables n=14 (11/3), APS/APACHE II n=334 (167/167). Abbreviations: IQR interquartile range; APACHE Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment. For comparisons between ALD and general ICU comparator cohort, all ALD cohort members were assumed to have a comorbid diagnosis of liver disease.

eTable 2. Baseline characteristics of ALD cohort who were matched and unmatched to the general ICU cohort.

		Unmatched	Matched	p-value
n		72 (2.9%)	2391 (97.1%)	
Age (years)	Median (IQR)	41.5 (37.5, 45)	53 (45, 61)	<0.001
Sex	Male	58 (80.6%)	1528 (63.9%)	0.004
	Female	14 (19.4%)	863 (36.1%)	
Socioeconomic status quintile	1 Least deprived	1 (1.4%)	224 (9.4%)	<0.001
	2	0 (0.0%)	278 (11.6%)	
	3	0 (0.0%)	388 (16.2%)	
	4	8 (11.1%)	523 (21.9%)	
	5 Most deprived	63 (87.5%)	978 (40.9%)	
Comorbidity count	1	69 (95.8%)	1889 (79.0%)	0.002
	2	3 (4.2%)	382 (16.0%)	
	3+	0 (0.0%)	120 (5.0%)	
Previous year inpatient hospital admissions	Median (IQR)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	0.95
	Mean (SD)	1.5 (2.0)	1.6 (2.5)	0.68
Previous year inpatient days in hospital	Median (IQR)	0.0 (0.0, 6.0)	1.0 (0.0, 13.0)	0.14
	Mean (SD)	4.9 (9.4)	11.1 (22.0)	0.027
Admission source	Theatre after emergency surgery	6 (8.5%)	379 (15.9%)	0.273
	Emergency department	19 (26.8%)	505 (21.1%)	
	Hospital ward	25 (35.2%)	746 (31.2%)	
	Other	21 (29.6%)	758 (31.7%)	
ICU admission diagnosis	Cardiovascular	16 (22.2%)	430 (18.0%)	0.559
	Respiratory	12 (16.7%)	536 (22.4%)	
	Gastrointestinal/liver	34 (47.2%)	994 (41.6%)	
	Renal	1 (1.4%)	30 (1.3%)	
	Neurological	6 (8.3%)	275 (11.5%)	
	Trauma	0 (0.0%)	55 (2.3%)	
	Other	3 (4.2%)	71 (3.0%)	
Acute Physiology Score	Median (IQR)	26 (23, 30)	17 (12, 23)	<0.001
APACHE II score	Median (IQR)	30 (26, 33)	22 (17, 28)	<0.001
Number of organ systems supported on ICU admission	0	7 (9.7%)	370 (15.5%)	0.001
	1	19 (26.4%)	1031 (43.1%)	
	2	35 (48.6%)	825 (34.5%)	
	3	11 (15.3%)	165 (6.9%)	
Mechanical ventilation	n (%)	61 (84.7%)	1847 (77.3%)	0.139
Circulatory support	n (%)	47 (65.3%)	1098 (46.0%)	0.001
Renal replacement therapy	n (%)	14 (19.4%)	231 (9.7%)	0.006
Liver SOFA score	0	4 (5.6%)	437 (18.3%)	<0.001
	1	6 (8.3%)	289 (12.1%)	
	2	19 (26.4%)	774 (32.4%)	
	3	20 (27.8%)	334 (14.0%)	
	4	15 (20.8%)	222 (9.3%)	
	Missing	8 (11.1%)	335 (14.0%)	
ICU length of stay (days)	Median (IQR)	1.9 (0.7, 7.5)	2.7 (1.0, 7.3)	0.24
Index hospital length of stay (days)	Median (IQR)	6.0 (2.0, 28.5)	12.0 (5.0, 29.0)	0.005
ICU mortality	n (%)	43 (59.7%)	1044 (43.7%)	0.007
Hospital mortality	n (%)	50 (69.4%)	1398 (58.5%)	0.062

Missing data Total (general unmatched/matched): admission source n=4 (1/3), organ support variables n=3 (0/3), APS/APACHE II n=172 (5/167). Abbreviations: IQR interquartile range; APACHE Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment.

eTable 3. Independent factors associated with early and late mortality in the ALD cohort (in full).

Characteristic	Characteristic	5-year death (%)	Early 0-30d death (%)	Late 31d-5y death (%)	Early Multivariable regression HR (95%CI) p-value	Late Multivariable regression HR (95%CI) p-value
n		2463	2463	1106		
Age (years)	per 10 year increase	-	-	-	1.24 (1.19, 1.29) <0.001	1.33 (1.19, 1.50) <0.001
Sex	Male	83.3%	54.0%	57.5%	1 (Reference)	1 (Reference)
	Female	81.9%	56.7%	49.2%	1.02 (0.92, 1.13) 0.652	0.73 (0.58, 0.93) 0.010
Socioeconomic status quintile	1 Least deprived	85.0%	56.0%	59.5%	1 (Reference)	1 (Reference)
	2	80.2%	52.5%	52.0%	1.01 (0.64, 1.57) 0.978	0.75 (0.61, 0.91) 0.004
	3	84.1%	49.5%	63.8%	1.03 (0.67, 1.58) 0.885	1.08 (0.80, 1.46) 0.622
	4	84.5%	58.2%	55.3%	1.19 (0.77, 1.85) 0.438	0.89 (0.55, 1.45) 0.642
	5 Most deprived	81.7%	55.7%	50.2%	1.11 (0.75, 1.63) 0.601	0.78 (0.55, 1.09) 0.140
Comorbidity count	0	82.4%	55.0%	53.9%	1 (Reference)	1 (Reference)
	1	83.6%	55.3%	55.3%	1.13 (0.99, 1.30) 0.063	0.78 (0.61, 0.99) 0.043
	2	86.1%	55.1%	63.3%	1.18 (0.78, 1.79) 0.432	1.07 (0.69, 1.68) 0.758
	3+	87.3%	48.4%	72.0%	1.12 (0.72, 1.75) 0.621	1.04 (0.63, 1.73) 0.871
Previous year hospital admissions	0	82.4%	58.9%	47.7%	1 (Reference)	1 (Reference)
	1	81.5%	54.4%	52.0%	0.96 (0.86, 1.09) 0.550	1.25 (0.91, 1.71) 0.172
	2	84.7%	54.6%	61.1%	0.97 (0.80, 1.18) 0.775	1.69 (1.03, 2.79) 0.039
	3	84.5%	48.9%	65.3%	0.93 (0.77, 1.12) 0.448	2.19 (1.34, 3.55) 0.002
	4+	83.8%	47.2%	64.5%	0.89 (0.72, 1.10) 0.283	1.76 (1.12, 2.77) 0.015
Admission source	Theatre after emergency surgery	79.4%	47.3%	53.9%	1 (Reference)	1 (Reference)
	Emergency department	77.0%	47.3%	47.8%	0.97 (0.83, 1.13) 0.694	0.76 (0.52, 1.10) 0.143
	Hospital ward	87.2%	63.8%	58.1%	1.13 (0.96, 1.33) 0.138	1.08 (0.81, 1.45) 0.587
	Other	83.8%	55.1%	57.8%	1.08 (0.90, 1.28) 0.415	1.00 (0.64, 1.57) 0.997
ICU admission diagnosis	Variceal bleed	78.7%	42.4%	57.8%	1.89 (1.14, 3.15) 0.014	1 (Reference)
	Pneumonia	83.0%	54.1%	56.5%	1.67 (1.05, 2.66) 0.031	1.08 (0.64, 1.84) 0.767
	Septic shock	88.0%	67.6%	54.1%	1.90 (1.04, 3.49) 0.037	1.05 (0.50, 2.17) 0.905
	Liver failure	89.7%	73.0%	53.5%	2.16 (1.17, 3.99) 0.013	1.01 (0.72, 1.41) 0.960
	Post-cardiac arrest	93.4%	80.9%	57.6%	3.23 (1.93, 5.40) <0.001	1.04 (0.65, 1.67) 0.877
	Seizures	70.9%	26.0%	57.4%	1 (Reference)	1.80 (1.05, 3.10) 0.034
	Other	71.4%	49.2%	51.8%	1.91 (1.32, 2.77) 0.001	1.04 (0.72, 1.51) 0.819
Acute Physiology Score	per 10 point increase	-	-	-	1.83 (1.66, 2.02) <0.001	0.89 (0.74, 1.07) 0.205
Number of organs supported at admission	0	71.4%	33.2%	52.5%	1 (Reference)	1 (Reference)
	1	81.1%	48.0%	58.0%	1.39 (1.18, 1.64) <0.001	1.36 (1.06, 1.74) 0.016
	2	87.9%	68.0%	52.6%	1.94 (1.69, 2.23) <0.001	1.23 (1.06, 1.42) 0.007
	3	89.8%	79.0%	37.0%	2.12 (1.50, 3.01) <0.001	0.80 (0.55, 1.16) 0.237
Liver SOFA score	0	70.4%	36.7%	46.1%	1 (Reference)	1 (Reference)
	1	78.2%	46.1%	53.2%	1.20 (0.98, 1.46) 0.070	1.20 (0.82, 1.75) 0.355
	2	83.4%	55.6%	55.6%	1.79 (1.40, 2.30) <0.001	1.42 (1.11, 1.81) 0.006
	3	88.7%	65.5%	61.5%	2.19 (1.76, 2.72) <0.001	1.98 (1.53, 2.57) <0.001
	4	93.4%	77.6%	63.4%	2.92 (2.29, 3.73) <0.001	2.02 (1.36, 2.99) <0.001
	Missing	85.9%	57.7%	60.7%	2.09 (1.54, 2.84) <0.001	1.66 (1.32, 2.10) <0.001

Kaplan-Meier estimator presented for % death. Multivariable Cox models are stratified by health board of residence. HR, hazard ratio; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment. Shaded rows are additional to abbreviated Table 2 in main manuscript.

eTable 4. Factors associated with first emergency hospital readmission in ALD cohort. Multivariable Fine and Gray regression with death modelled as a competing risk. Cumulative incidence function for 5-year emergency readmission presented as %.

		CIF (%) 5y readmission	Multivariable regression HR (95%CI) p-value
Age (years)	per 10 years	-	0.93 (0.88, 0.99) 0.032
Sex	Male	82.0%	1 (Reference)
	Female	86.2%	0.98 (0.89, 1.08) 0.684
Socioeconomic status quintile	1 Least deprived	83.6%	1 (Reference)
	2	84.4%	0.81 (0.60, 1.10) 0.173
	3	83.4%	0.98 (0.65, 1.47) 0.917
	4	80.9%	0.88 (0.57, 1.35) 0.548
	5 Most deprived	83.9%	0.81 (0.61, 1.08) 0.148
Comorbidity count	0	81.7%	1 (Reference)
	1	90.3%	1.12 (0.89, 1.40) 0.347
	2	93.7%	1.25 (0.98, 1.60) 0.075
	3+	75.6%	0.82 (0.39, 1.71) 0.596
Previous year inpatient hospital admissions	0	75.2%	1 (Reference)
	1	83.4%	1.21 (1.02, 1.43) 0.025
	2	89.5%	1.56 (1.26, 1.94) <0.001
	3	89.0%	1.97 (1.20, 3.23) 0.007
	4+	92.9%	2.95 (2.12, 4.10) <0.001
Admission source	Theatre after emergency surgery	83.4%	1 (Reference)
	Emergency department	80.4%	0.95 (0.69, 1.31) 0.755
	Hospital ward	85.0%	0.95 (0.71, 1.28) 0.746
	Other	84.9%	1.07 (0.82, 1.40) 0.621
ICU admission diagnosis	Variceal bleed	90.3%	1 (Reference)
	Pneumonia	84.0%	0.78 (0.67, 0.91) 0.002
	Septic shock	76.9%	0.75 (0.50, 1.12) 0.159
	Liver failure	89.5%	1.00 (0.79, 1.27) 0.983
	Post-cardiac arrest	75.6%	0.80 (0.56, 1.13) 0.205
	Seizures	94.0%	0.81 (0.66, 1.00) 0.049
	Other	78.8%	0.75 (0.59, 0.94) 0.013
Acute Physiology Score	per 10 points	-	0.88 (0.77, 0.99) 0.034
Number of organ systems supported during ICU admission	0	81.6%	1 (Reference)
	1	88.6%	1.21 (1.02, 1.43) 0.030
	2	78.2%	1.09 (0.87, 1.36) 0.464
	3	85.8%	1.32 (1.11, 1.57) 0.002
Liver SOFA score	0	75.6%	1 (Reference)
	1	82.7%	1.12 (0.83, 1.51) 0.460
	2	90.8%	1.20 (0.92, 1.59) 0.184
	3	86.6%	1.45 (1.16, 1.81) 0.001
	4	76.8%	1.00 (0.53, 1.90) 0.999
	Missing	85.1%	1.06 (0.90, 1.23) 0.495

eTable 5. Baseline characteristics of ALD cohort stratified by presence of cirrhosis.

		Non cirrhosis	Cirrhosis	p-value
n		831 (33.7%)	1632 (66.3%)	
Age (years)	Median (IQR)	54 (45, 62)	52 (44, 60)	<0.001
Sex	Male	547 (65.8%)	1039 (63.7%)	0.290
	Female	284 (34.2%)	593 (36.3%)	
Socioeconomic status quintile	1 Least deprived	74 (8.9%)	151 (9.3%)	0.863
	2	96 (11.6%)	182 (11.2%)	
	3	122 (14.7%)	266 (16.3%)	
	4	181 (21.8%)	350 (21.4%)	
	5 Most deprived	358 (43.1%)	683 (41.9%)	
Comorbidity count excluding liver comorbidities	0	649 (78.1%)	1309 (80.2%)	0.454
	1	138 (16.6%)	247 (15.1%)	
	2	35 (4.2%)	54 (3.3%)	
	3+	9 (1.1%)	22 (1.3%)	
Previous year inpatient hospital admissions	Median (IQR)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	<0.001
	Mean (SD)	1.4 (2.5)	1.7 (2.4)	0.002
Previous year inpatient days in hospital	Median (IQR)	0.0 (0.0, 6.0)	2.0 (0.0, 16.0)	<0.001
	Mean (SD)	7.7 (19.5)	12.7 (22.7)	<0.001
Admission source	Theatre after emergency surgery	99 (11.9%)	286 (17.6%)	<0.001
	Emergency department	221 (26.6%)	303 (18.6%)	
	Hospital ward	256 (30.8%)	515 (31.6%)	
	Other	254 (30.6%)	525 (32.2%)	
ICU admission diagnosis	Cardiovascular	212 (25.5%)	234 (14.3%)	<0.001
	Respiratory	244 (29.4%)	304 (18.6%)	
	Gastrointestinal/liver	142 (17.1%)	886 (54.3%)	
	Renal	20 (2.4%)	11 (0.7%)	
	Neurological	139 (16.7%)	142 (8.7%)	
	Trauma	36 (4.3%)	19 (1.2%)	
	Other	38 (4.6%)	36 (2.2%)	
Acute Physiology Score	Median (IQR)	19 (14, 24)	17 (12, 23)	<0.001
APACHE II score	Median (IQR)	22 (17, 27)	23 (18, 29)	<0.001
Number of organ systems supported on ICU admission	0	115 (13.8%)	262 (16.1%)	0.002
	1	323 (38.9%)	727 (44.5%)	
	2	323 (38.9%)	537 (32.9%)	
	3	70 (8.4%)	106 (6.5%)	
Mechanical ventilation	n (%)	652 (78.6%)	1256 (77.1%)	0.399
Circulatory support	n (%)	433 (52.2%)	712 (43.7%)	<0.001
Renal replacement therapy	n (%)	94 (11.3%)	151 (9.3%)	0.106
Liver SOFA score	0	289 (34.8%)	152 (9.3%)	<0.001
	1	148 (17.8%)	147 (9.0%)	
	2	191 (23.0%)	602 (36.9%)	
	3	62 (7.5%)	292 (17.9%)	
	4	20 (2.4%)	217 (13.3%)	
	Missing	121 (14.6%)	222 (13.6%)	
ICU length of stay (days)	Median (IQR)	2.8 (1.0, 8.6)	2.7 (1.0, 7.0)	0.099
Index hospital length of stay (days)	Median (IQR)	12.0 (4.0, 33.0)	12.0 (5.0, 28.0)	0.560
ICU mortality	n (%)	337 (40.6%)	750 (46.0%)	0.011
Hospital mortality	n (%)	428 (51.5%)	1020 (62.5%)	<0.001

Missing data: admission source n=4, organ support variables n=3, APS n=172, APACHE II score n=172.
Abbreviations: IQR interquartile range; APACHE Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment.

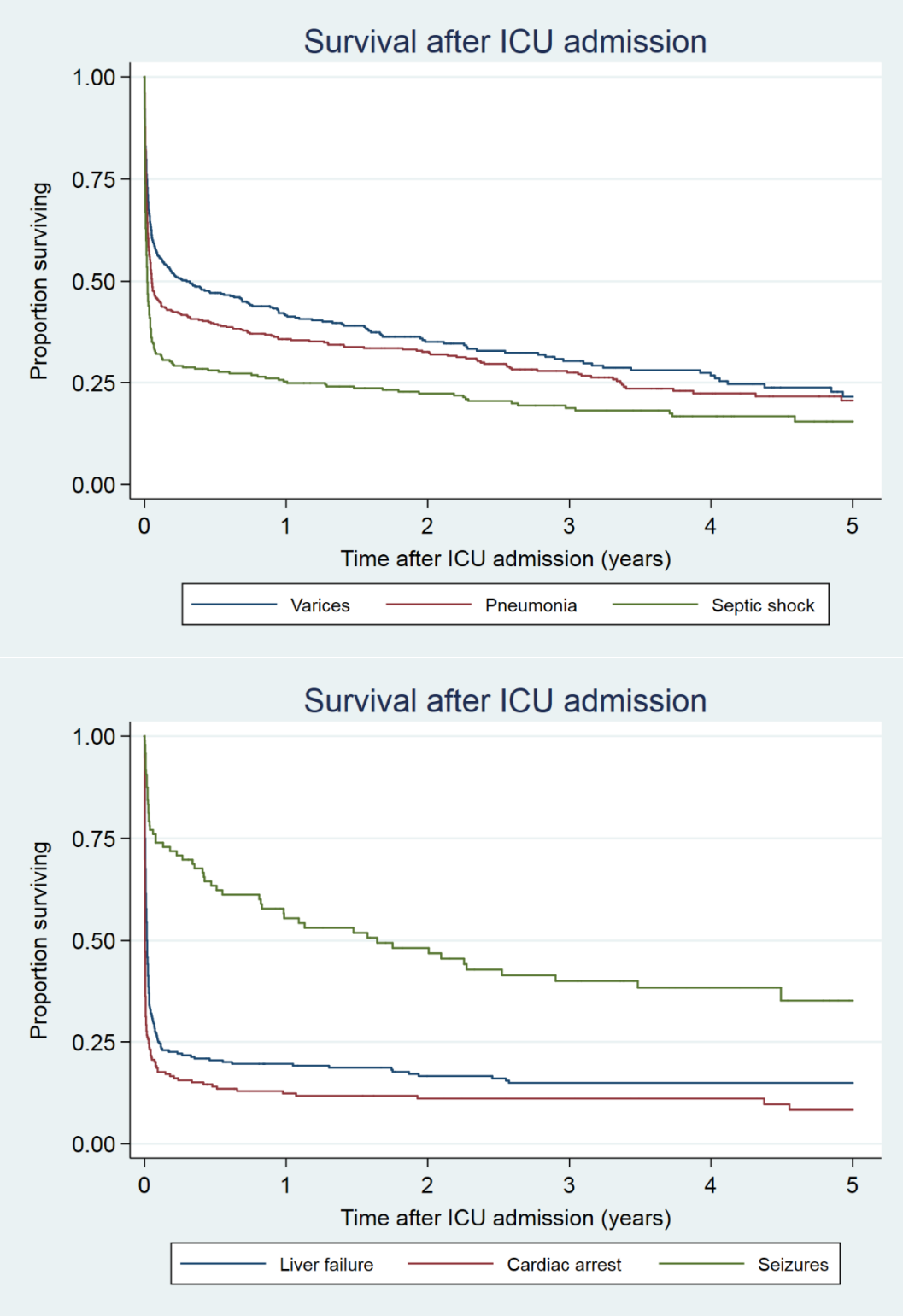
eTable 6. Mortality and resource use outcomes for ALD cohort stratified by presence of cirrhosis. 95% confidence intervals (95%CI) are Poisson CIs for readmission rates and are derived by bootstrapping for days in hospital and costs.

	Whole cohort	Non-cirrhosis	Cirrhosis
n (%)	2463 (100%)	831 (33.7%)	1632 (66.3%)
30 day mortality % (95%CI)	54.9 (53.0, 56.9)	47.9 (56.1, 60.9)	58.5 (56.6, 61.4)
5 year mortality % (95%CI)	79.2 (77.2, 81.2)	71.3 (67.5, 74.9)	83.3 (80.1, 85.6)
30 day emergency readmission CIF % (95%CI)	21.7 (19.2, 24.3)	14.3 (11.1, 17.9)	26.6 (23.1, 30.2)
5 year emergency readmission CIF % (95%CI)	83.4 (80.1, 86.3)	77.4 (71.6, 82.2)	87.5 (83.3, 90.7)
5 year emergency readmission rate per person year (95% CI)	1.64 (1.59, 1.70)	1.46 (1.39, 1.54)	1.79 (1.72, 1.87)
5 year total days in hospital during emergency readmissions per person year (95% CI)	14.4 (13.0, 15.9)	11.4 (9.2, 13.7)	16.8 (14.6, 19.1)
5 year costs from emergency readmissions per person per year (95% CI) (GBP£ and USD$)	£9725 (£8745, £10705)	£7715 (£6210, £9220)	£11360 (£9844, £12876)
	$13834 ($12440, $15228)	$10974 ($8834, $13115)	$16159 ($14003, $18316)

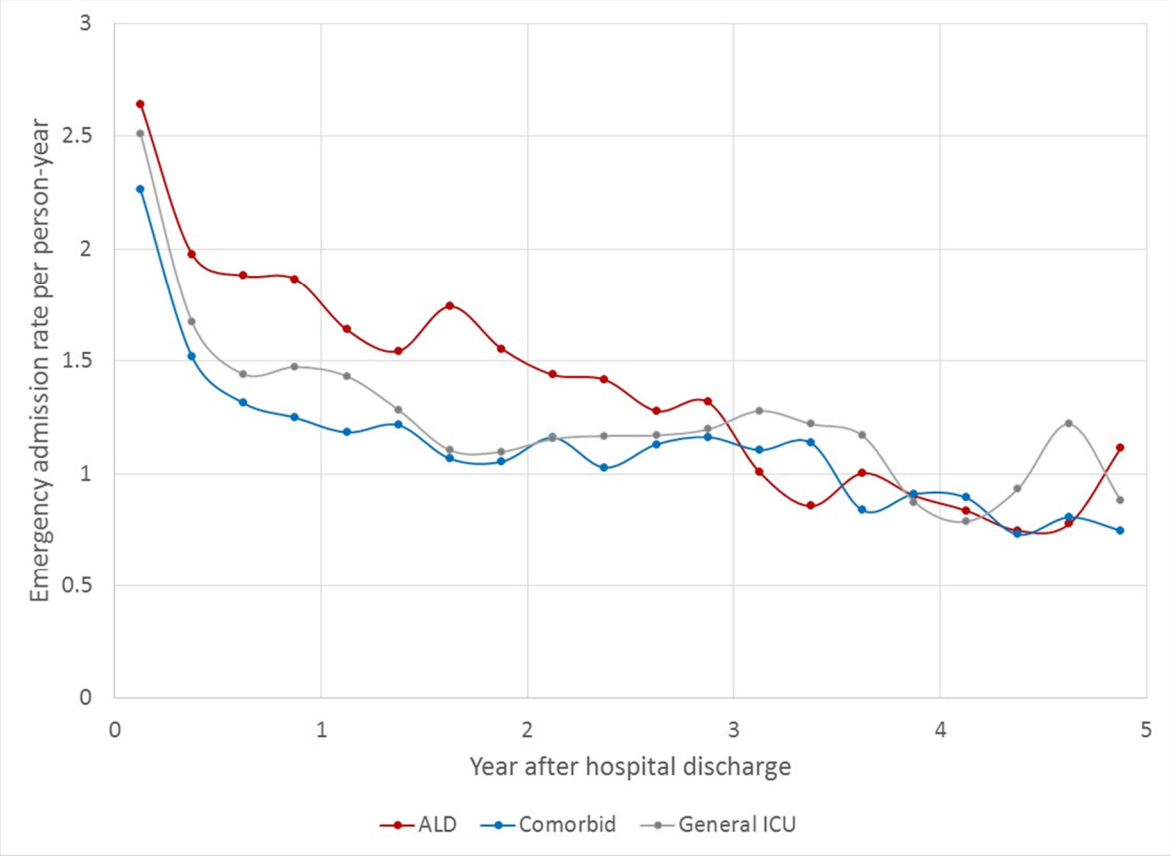
eTable 7. Mortality and resource use outcomes for ALD cohort relative to severe comorbid cohort: comparison of multivariable unmatched and matched analysis. To illustrate the robustness of multivariable unmatched analyses, we conducted additional multivariable analyses in a matched comorbid cohort (matching on age, sex, socioeconomic status, comorbidity count, admission source) for the five outcomes reported in the main manuscript adjusted for potential confounders. This demonstrated that point estimates were very similar between unmatched and matched multivariable analyses but suffered from loss of precision due to the smaller sample size. HR, hazard ratio; 95%CI, 95% confidence intervals.

	Primary unmatched analysis	Matched analysis
n (%) in ALD cohort	2463 (100%)	1513 (61.4%)
5 year mortality HR (95%CI)	1.31 (1.17, 1.47)	1.32 (1.16, 1.51)
Early mortality HR (95%CI)	1.28 (1.09, 1.51)	1.30 (1.06, 1.58)
Late mortality HR (95%CI)	1.37 (1.28, 1.47)	1.43 (1.31, 1.56)
5 year emergency readmission HR (95%CI)	0.99 (0.92, 1.07)	0.98 (0.89, 1.08)
5 year emergency readmission Rate ratio (95%CI)	1.32 (1.17, 1.48)	1.27 (1.10, 1.47)

eFigure 1. Kaplan-Meier plots of survival in ALD cohort stratified by six commonest ICU admission diagnoses in the ALD cohort from time of ICU admission. Plotted on two separate graphs for ease of reading.



eFigure 2. Emergency hospital readmission rate in ALD cohort compared with comparator cohorts with other severe comorbidities and matched general ICU patients during five-year follow up after hospital discharge.



eFigure 3. Cost of emergency hospital readmissions in ALD cohort stratified by diagnosis on admission. Lines are stacked so that the upper most line reflects total costs of the three categories diagnosis (liver-related, alcohol-related and other diagnoses).